Original Article

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Development of a Prediction Model for Acute Kidney Injury after Colistin Treatment for Multidrug-resistant *Acinetobacter baumanii* Ventilator-Associated Pneumonia: A Pilot Study

Dussadee Seanglaw, M.D.[1], Thotsaporn Morasert, M.D.[2]

[1]Department of Internal Medicine, Suratthani Hospital, Mueang, Surat Thani 84000, Thailand.

[2]Pulmonary and Critical Care Medicine, Department of Internal Medicine, Suratthani Hospital, Mueang, Surat Thani 84000, Thailand.

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Abstract:

Objective: Multidrug-resistant *Acinetobacter baumanii* (MDR-AB) ventilator-associated pneumonia (VAP) is the major complication following hospital admission in Thailand, increasing morbidity and prolonging hospital stay duration. Treatment of MDR-AB VAP usually requires colistin which has highly nephrotoxic properties. Therefore, we aimed to develop a pilot prediction model for acute kidney injury (AKI) after colistin treatment.

Material and Methods: We conducted a retrospective cohort study. All MDR-AB VAP patients who received colistin for at least 72 hours in Suratthani Hospital from January to July 2017 were eligible for inclusion. The primary outcome was the overall presence of AKI on days 3, 5 or 7 after colistin administration. Multivariable logistic regression analysis was used to develop the final prediction model.

Results: Of 85 MDR-AB VAP patients, 51 (61%) developed AKI after colistin treatment. Nine factors, female, intensive care unit (ICU) admission, diabetes mellitus, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum sodium, creatinine, blood urea nitrogen (BUN) and glomerular filtration rate were potential predictors of AKI. Multivariable logistic regression with backward stepwise selection revealed the best prediction model had four predictors: female, ICU admission, BUN, and DBP. The area under the receiver operating characteristic curve for the model in predicting AKI among MDR-AB VAP patients was 0.801 (95% confidence interval: 0.703, 0.898).

Contact: Thotsaporn Morasert, M.D.
Pulmonary and Critical Care Medicine, Department of Internal Medicine,
Suratthani Hospital, Mueang, Surat Thani 84000, Thailand.
E-mail: thot_kwan@hotmail.com

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Conclusion: The prediction model containing four predictors, female gender, ICU admission, BUN level, and DBP had fair to good performance in predicting AKI after colistin treatment among MDR-AB VAP patients.

Keywords: acute kidney injury, colistin, prediction model, ventilator-associated pneumonia

Introduction

Ventilator-associated pneumonia (VAP), defined as pneumonia developing after 48 to 72 hours of intubation, is a leading medical problem such as complicated hospitalization, prolonged mechanical ventilation, and higher mortality.[1] In 2016-2018, the incidence of VAP in Thailand was reported from 18.9% in a medical intensive care unit (ICU)[2] to 28.7% in a mixed ICU.[3] *Acinetobacter baumannii* (AB) is an aerobic non-fermenting gram-negative coccobacilli bacteria which has become one of the most common causative organisms of VAP, with resistance to a large number of antibiotics.[4] Multidrug-resistant *Acinetobacter baumannii* (MDR-AB) has been reported at incidences from 38.7% to 69.3%[2,5], causing high VAP mortality and treatment-associated adverse effects.

The antibiotic colistin has been increasingly used in recent years to treat MDR-AB. Because of the resistance of MDR-AB to almost all the other antibiotics classes, including carbapenems.[4] Colistin has bactericidal effects through penetration and electrostatic interaction with the lipopolysaccharide layers of the gram-negative bacterial cell membrane resulting in cell content leakage and death.[6] Although colistin is an effective antibiotic in MDR-AB treatment[7], it has also been associated with incidences of nephrotoxicity or acute kidney injury (AKI) of up to 40.0%.[6,8-11]

There have been several studies which have examined the factors associated with AKI after colistin treatment, which included age[8,12-15], male gender[11], actual body weight[9,15], the dose of colistin per ideal body weight (IBW)[10,12], Charlson's comorbidity index[12,16], diabetes mellitus[9,10,12,14,15], chronic obstructive pulmonary disease[14], renal disease[16], liver disease[12,13], septic shock[12], Acute Physiology and Chronic Health Evaluation (APACHE) II score[17,18], SAPS II score[19,20], ICU setting[10,19,21], initial creatinine level[16], hematocrit level[12,13], albumin level <2 g/dL[11,21], serum bilirubin level >5 mg/dL[11], delay of treatment[22], and receiving concomitant nephrotoxic agents.[10]

Although there are various strong predictors for the development of AKI after receiving colistin, we still lack a bedside prediction tool for assisting the clinician's decision about AKI probability after colistin treatment. Therefore, this pilot study aimed to explore potential predictors and develop a prediction model to prognosticate AKI risk for an individual MDR-AB VAP patient receiving colistin treatment.

Material and Methods

The Ethics Committee of Suratthani Hospital approved the study protocol (Approval ID. 24/2563). We conducted and reported the study following the Tripod (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) statement.[23]

Study design and setting

The study was a retrospective cohort study conducted in Suratthani Hospital, a tertiary care centre in the south of Thailand.

Participants

We screened all hospitalized adult patients in general medical wards and medical intensive care units (ICU) who were mechanically ventilated and received intravenous colistin treatment for MDR-AB VAP between January and July 2017. The eligible cases were reviewed and the

VAP diagnosis was confirmed according to the National Healthcare Safety Network criteria.[24] Identification of AB was done using a standard semi-quantitative culture.[25] An AB infection was classified as MDR if it was resistant to more than two of five classes of antibiotics.[26] Our colistin susceptibility testing was performed with the automated Vitek®2 system based on the broth microdilution minimum inhibitory concentration technique. Colistin resistance was defined as a minimum inhibitory concentration breakpoint of more than two µg/ml. The exclusion criteria were 1) colistin treatment duration of fewer than 72 hours, 2) prior colistin administration in the current admission, and/or 3) end-stage renal disease (glomerular filtration rate [GFR] < 15 ml/min/1.73 m^2) or on renal replacement therapy due to AKI.

Definitions and Outcome measurements

The primary outcome was the overall presence of AKI on days 3, 5 or 7 after initiation of colistin compared to the day before starting the colistin. AKI was defined using the KDIGO guideline as any of the following after colistin administration: increase in serum creatinine (SCr) by ≥0.3 mg/dl within 48 hours, increase in SCr to ≥1.5 times baseline, or urine volume <0.5 ml/kg/hr for 6 hours.[27] The GFR was calculated using the Cockcroft and Gault formula.

Predictors

Baseline demographic and clinical data including age, gender, height, body weight, underlying diseases, and ward (ICU vs general ward) were collected from the clinical charts. In addition, the following clinical and laboratory parameters were collected at the time of initiation of colistin: vital signs, urine output (millilitres), fluid balance (amount of fluid intake minus output), hemodialysis initiation, complete blood count, serum electrolytes, glucose, blood urea nitrogen (BUN) and SCr. Colistin administration data, including duration and dosage, were collected.

Other scoring systems

Other scoring system results included in the analysis were 1) for general severity of illness, APACHE II; 2) pneumonia-specific scoring systems: CURB-65 (Confusion, Uremia, Respiratory rate, Blood pressure, age ≥65 years), Clinical Pulmonary Infection Score (CPIS), pneumonia severity index (PSI), PIRO-VAP (Predisposition, Insult, Response, Organ dysfunction); and 3) the Charlson Comorbidity Index. The study investigators reviewed and calculated the scores from these instruments at the initiation of colistin.

Colistin administration

The intravenous colistin (colistimethate sodium [CMS], Manufac) formulation was supplied in vials containing 150 mg colistin base activity (4.5 million international units of CMS) per vial. The manufacturer's recommended dose for colistin is 2.5 to 5 mg/kg per day of colistin base activity for patients with normal renal function, not to exceed 300 mg daily.[28] The loading dose of colistin was defined as administering 300 mg of colistin before the maintenance dose. The attending physician decided on the initiation, dosage and time of cessation of colistin.

Statistical analysis

We explored the potential predictors by comparing the clinical characteristics between AKI and non-AKI among the study MDR-AB VAP patients. Categorical variables are presented as percentages and compared using Fisher's exact test. Continuous variables are presented as mean (S.D.) and compared using a two-sample t-test. Non-parametric continuous variables are presented as median with interquartile range (IQR) and compared using the Wilcoxon Rank Sum (Mann-Whitney) test. All proportions and p-values were calculated among non-missing data. Statistical analyses were performed using Stata Statistical Software version 15.1 (Stata Corporation, College Station, Tex., USA).

Model development

Type of model

We used a multivariable logistic regression model to estimate the coefficient associated with each potential predictor in the derivation dataset.

Selection of predictors and scoring

First, the predictor-outcome association was examined using the area under the receiver operating characteristic curved (AUROC) and standardized differences (std-diff) to determine the covariate imbalance between the AKI and non-AKI groups. Second, we selected the predictors before modelling based on clinical knowledge, previous research, or if they met the following criteria: p-value<0.1, AUROC≥0.55 and std-diff≥0.1. Third, a multivariable logistic regression model with backward stepwise selection by removing parameters with a p-value more than 0.1 was used to determine the final model. The discrimination power of the final model was tested using the AUROC and plotted curve. The β-coefficients of each predictor were divided by the lowest coefficient and rounded up to the closest integer to generate score points.

Predictive performance of the prediction model

Calibration of the prediction model was assessed with the Hosmer-Lemeshow goodness of fit test. The discriminating ability of the prediction model to differentiate between AKI and non-AKI patients was evaluated using the AUROC (c-statistic).

Results

Overall, 173 eligible patients were identified. Of this number, eighty-eight patients were excluded (68 patients received colistin for less than 72 hours, 12 patients had previously received colistin during the current admission and 8 patients had previously been on renal replacement therapy due to AKI or end-stage renal disease). Finally, 85 patients were included in the final analysis. Fifty-one patients (61.0%) had AKI, and six of them (12.0%) had undergone hemodialysis during this admission.

Patient characteristics

A majority of patients were female (58.8%), with a mean age of 63.7 years (S.D. 19.4). Fifty-seven patients (67.1%) were admitted to the ICU during colistin initiation. The comparisons between baseline characteristics, clinical parameters and laboratory investigations of the study patients who received colistin treatment for AB-VAP (n=85) are shown in Table 1. In comparison between the AKI and non-AKI cases, the AKI cases were more likely to be female (73.0% vs 38.0%), have current diabetes mellitus (35.0% vs 15.0%), experience ICU admission during colistin initiation (78.0% vs 50.0%), have a higher BUN level (average 31 mg/dL vs 17 mg/dL), higher SCr (0.94 mg/dL vs 0.65 mg/dL), lower baseline GFR and higher in-hospital mortality (76.0% vs 53). There were no significant differences in the points of any of the scoring systems (Table 2), co-administration of other nephrotoxic drugs, administration of the loading dose or the daily dose of colistin (Table 3) between the AKI and non-AKI patients. However, the non-AKI patients had a longer means duration of colistin administration than the AKI patients (10 days vs 7 days). The characteristics and complications of the AKI patients are shown in Supplementary Table 1.

Multivariable logistic regression modelling

Finally, ten predictors were included in the final multivariable model: female gender, ICU admission, diabetes mellitus, SBP, DBP, serum sodium, SCr, BUN, GFR and administration of a loading dose of colistin. The univariable and multivariable clinical predictors with their odds ratios (OR), 95% confidence intervals (CI), β-coefficients and scoring are shown in Table 4. The prediction equation of AKI = (female*1.445) + (BUN*0.035) + (ICU admission*1.221) +

(DBP*0.034) – 4.725. ROC curve was plotted to demonstrate the discriminating ability of the prediction equation in AKI risk (Figure 1). The AUROC was 0.801 (95% CI: 0.703, 0.898). With the incidence of 61% in this study, the overall correct classification rate was estimated to be 71.8%, with 70.6% of the AKI cases correctly classified (sensitivity) and 73.5% of the non-AKI correctly classified (specificity). The positive and negative predictive values were 80.0% and 62.5%, respectively. The three ranges and cut-off points with their positive likelihood ratios are shown in Supplementary Table 2.

Table 1 Clinical characteristics and laboratory investigations of AKI and non-AKI patients who received colistin treatment for *A.baumanii* ventilator-associated pneumonia (n=85)

Factor	AKI (n=51)	Non-AKI (n=34)	p-value	AUROC (95%CI)
Female, n (%)	37 (72.6)	13 (38.2)	0.003	0.67 (0.56, 0.77)
Age, years, mean (S.D.)	65.3 (18.2)	61.3 (21.1)	0.360	0.55 (0.44, 0.66)
Actual body weight, kg, mean (S.D.)	60.7 (15.7)	58.5 (10.2)	0.480	0.52 (0.41, 0.63)
Underlying disease(s), n (%)				
Congestive heart failure	6 (11.8)	5 (14.7)	0.748	0.51 (0.41, 0.63)
Diabetes mellitus	18 (35.3)	5 (14.7)	0.047	0.60 (0.49, 0.70)
Hypertension	27 (52.9)	12 (35.3)	0.125	0.59 (0.48, 0.69)
Chronic kidney disease	14 (27.5)	4 (11.8)	0.110	0.58 (0.46, 0.68)
Cirrhosis	1 (2.0)	1 (2.9)	1.000	0.50 (0.38, 0.61)
ICU stay, n (%)	42 (82.3)	22 (64.7)	0.077	0.59 (0.48, 0.69)
BT, ºC, mean (S.D.)	38.0 (1.0)	38.1 (0.8)	0.430	0.52 (0.42, 0.64)
HR, per minute, mean (S.D.)	116.8 (20.4)	113.2 (16.3)	0.390	0.57 (0.46, 0.68)
SBP, mmHg, mean (S.D.)	117.5 (25.8)	108.9 (15.0)	0.082	0.59 (0.48, 0.69)
DBP, mmHg, mean (S.D.)	72.4 (15.0)	67.0 (9.9)	0.067	0.61 (0.50, 0.72)
RR, per minute, mean (S.D.)	24.8 (4.7)	24.0 (4.3)	0.420	0.55 (0.43, 0.65)
Urine output 24 hrs before colistin administration, ml/day, median (IQR)	1,140 (850, 1,900)	1,400 (1,100, 2,090)	0.230	0.58 (0.46, 0.68)
Length of stay, days, median (IQR)	22.0 (15.0, 35.0)	25.0 (18.0, 43.0)	0.230	–
Mortality, n (%)	39 (76)	18 (53)	0.034	–
Laboratory investigations				
WBC count, x 10^3 cells/mm^3, median (IQR)	14.5 (9.3, 19.4)	11.9 (10.1, 18.5)	0.500	0.53 (0.42, 0.64)
PMN, %, mean (S.D.)	83.5 (11.2)	83.5 (10.2)	0.990	0.51 (0.40, 0.62)
Hematocrit, %, mean (S.D.)	29.9 (6.1)	28.7 (4.8)	0.330	0.52 (0.41, 0.63)
Platelets, x 10^3 cells/mm^3, median (IQR)	220 (144, 357)	294.5 (180, 385)	0.340	0.56 (0.45, 0.67)
Sodium, mmol/L, mean (S.D.)	141.6 (8.5)	138.2 (8.4)	0.075	0.60 (0.49, 0.70)
Potassium, mmol/L, mean (S.D.)	4.0 (0.7)	3.9 (0.7)	0.670	0.53 (0.42, 0.64)
Bicarbonate, mmol/L, mean (S.D.)	25.9 (6.7)	25.6 (6.5)	0.800	0.51 (0.40, 0.62)
Blood urea nitrogen, mg/dL, median (IQR)	31 (23, 48)	17 (12, 29)	<0.001	0.70 (0.60, 0.80)
Creatinine, mg/dL, median (IQR)	0.94 (0.70, 2.07)	0.65 (0.48, 0.88)	0.003	0.69 (0.58, 0.78)
GFR, ml/minute/1.73 m^2, median (IQR)	47.8 (30.6, 78.7)	79.8 (47.0, 142.9)	0.006	0.70 (0.58, 0.79)
Albumin, g/dl,	2.5 (0.8)	2.8 (0.6)	0.1203	0.62 (0.52, 0.73)

A.baumanii=Acinetobacter baumanii, AKI=acute kidney injury, AUROC=area under the receiver operating characteristic curve, CI=confidence interval, ICU=intensive care unit, IQR=interquartile range, S.D.=standard deviation, BT=body temperature, HR=heart rate, SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, RR=respiratory rate, WBC=white blood cells, PMN=polymorphonuclear neutrophils, GFR=glomerular filtration rate

Table 2 The scoring system points of AKI and non-AKI study patients with *A.baumanii* ventilator-associated pneumonia (n=85)

Scoring system, points	AKI (n=51)	Non-AKI (n=34)	p-value	AUROC (95%CI)
APACHE II, mean (S.D.)	12.0 (4.9)	12.1 (4.6)	0.900	0.51 (0.41, 0.63)
CPIS, mean (S.D.)	6.1 (1.4)	5.7 (1.2)	0.190	0.58 (0.46, 0.68)
CURB-65, median (IQR)	3 (2, 3)	2 (1, 3)	0.052	0.62 (0.51, 0.73)
PSI, mean (S.D.)	97.4 (42.5)	100.1 (27.0)	0.720	0.56 (0.45, 0.67)
PIRO-VAP, median (IQR)	1 (1, 2)	1 (0, 2)	0.427	0.55 (0.44, 0.66)
Charlson Comorbidity Index, median (IQR)	1 (0, 3)	1 (0, 2)	0.121	0.59 (0.49, 0.70)

A.baumanii=Acinetobacter baumanii, AKI=acute kidney injury, AUROC=area under the receiver operating characteristic curve, CI=confidence interval, S.D.=standard deviation, IQR=interquartile range, APACHE=Acute Physiology and Chronic Health Evaluation, CPIS=Clinical Pulmonary Infection Score, CURB-65=Confusion Uremia Respiratory rate Blood pressure and Age ≥65 years, PSI=Pneumonia Severity Index, PIRO-VAP=Predisposition Insult Response and Organ dysfunction score

Table 3 Comparison of colistin and other medications administration between AKI and non-AKI study patients with *A.baumanii* ventilator-associated pneumonia (n=85)

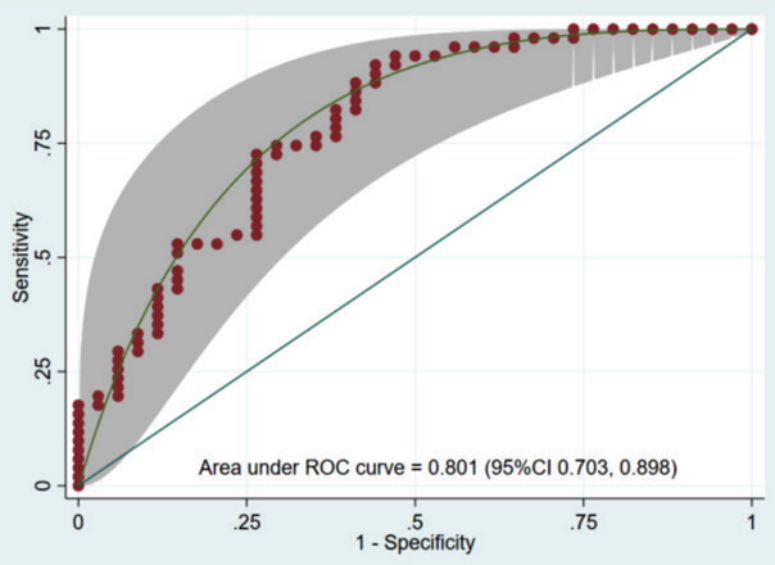
Factor	AKI (n=51)	Non-AKI (n=34)	p-value	AUROC (95%CI)
Fluid balance the first day, ml, mean (S.D.)	840 (0, 1452)	420 (0, 1040)	0.343	0.56 (0.45, 0.67)
Co-administration of nephrotoxic agent, n (%)	9 (18)	6 (18)	1.000	0.53 (0.42, 0.64)
ACE inhibitor	2 (4)	1 (3)	1.000	-
Radiographic contrast agent	3 (6)	3 (9)	0.680	-
Aminoglycoside	2 (4)	2 (6)	1.000	-
Amphotericin B	1 (2)	0 (0)	1.000	-
Vasopressor	7 (21)	26 (51)	0.006	-
Colistin administration				
Duration, days, mean (S.D.)	7.0 (3.8)	10.4 (4.7)	<0.001	-
Loading dose, 300 mg of colistin n (%)	31 (61)	28 (82)	0.054	0.61 (0.50, 0.72)
Daily dose, mg*, mean (S.D.)				
Actual	255.4 (73.0)	274.1 (63.9)	0.230	0.57 (0.45, 0.67)
Per kilogram of ABW	4.5 (1.7)	4.8 (1.4)	0.330	0.57 (0.45, 0.67)
Per kilogram of IBW	5.1 (1.6)	5.1 (1.4)	0.900	0.51 (0.40, 0.62)
Overdose, n (%)	8 (16)	2 (6)	0.300	0.55 (0.44, 0.66)
Underdose, n (%)	13 (25)	4 (12)	0.170	0.56 (0.45, 0.67)

A.baumanii=Acinetobacter baumanii, AKI=acute kidney injury, AUROC=area under the receiver operating characteristic curve, CI=confidence interval, S.D.=standard deviation, ACE=angiotensin-converting enzyme, ABW=actual body weight, IBW=ideal body weight
*milligrams colistin base activity

Table 4 Multivariable clinical predictors in the prediction of AKI in *A.baumanii* ventilator-associated pneumonia study patients

Prognostic indicator	Univariable analysis		Multivariable analysis			Score (points)
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	β-coefficient	
Female gender	4.27 (1.69-10.77)	0.002	4.24 (1.53, 11.73)	0.005	1.445	40
ICU stay	2.55 (0.93-6.96)	0.069	3.39 (1.02, 11.33)	0.047	1.221	35
Diabetes mellitus	3.16 (1.04-9.59)	0.042	-	-	-	-
SBP (every 1 mmHg increase)	1.02 (1.00-1.04)	0.090	-	-	-	-
DBP (every 1 mmHg increase)	1.03 (1.00-1.07)	0.071	1.04 (0.99, 1.08)	0.089	0.034	1
Sodium (every 1 mmol/L increase)	1.05 (0.99-1.11)	0.080	-	-	-	-
Creatinine (every 1 mg/dL increase)	1.70 (1.02, 2.84)	0.041	-	-	-	-
BUN (every 1 mg/dL increase)	1.03 (1.01, 1.06)	0.014	1.04 (1.01, 1.07)	0.016	0.035	1
GFR (every 1 ml/minute/1.73 m^2 increase)	0.99 (0.98-1.00)	0.006	-	-	-	-
Loading dose, 300 mg of colistin	0.33 (0.12-0.95)	0.039	-	-	-	-
Constant	-	-	-	-	-4.725	-

A.baumanii=Acinetobacter baumanii, Predicted equation of AKI=(female*1.445) + (BUN*0.035) + (ICU stay*1.221) + (DBP*0.034) - 4.725
AKI=acute kidney injury, OR=odds ratio, CI=confidence interval, ICU=intensive care unit, SBP=systolic blood pressure, DBP=diastolic blood pressure, BUN=blood urea nitrogen



ROC=receiver operating characteristic curve, CI=confidence interval

Figure 1 Receiver operating characteristic curve and confidence band of the study prediction model for prediction of acute kidney injury in *A.baumanii* ventilator-associated pneumonia study patients

Discussion

We developed an AKI prediction model after colistin administration among MDR-AB VAP patients. In this study, the incidence of AKI during the first seven days of colistin treatment was 63.5%, which is higher than previous studies which reported that AKI developed in approximately 50% of cases[8,9], but lower than a study on critically ill patients who developed AKI (75.2%).[29] The definition of AKI in this study used the KDIGO criteria[27], which is different from most previous studies that used the older risk, injury, failure, loss of kidney function, and end-stage kidney disease and AKIN criteria.[30]

This study was a pilot study of prediction model development and showed fair performance (AUROC=0.79) in predicting AKI after colistin for the individual patient. Our study finally selected a combination of 4 predictors to predict AKI after colistin treatment. The individual predictors were similar to previous studies, including female, ICU admission[10,19,21], DBP[31], and BUN.[5] Among these factors, there were some modifiable predictors/risk factors. Thus, if we can predict those patients who have a higher chance of nephrotoxicity after colistin, this prediction tool might impact the decision of the physician in terms of providing a more careful patient follow-up, avoiding a loading dose of colistin, optimizing the volume status and blood pressure during colistin treatment or even choice the other susceptible antibiotics such as tigecycline- or sulbactam-based therapies.

Among the selected predictors, one study reported that male gender was a risk factor for AKI after colistin treatment[11], but KDIGO 2012[32] and a recent meta-analysis of 83 studies reported[33] that female gender was a strong risk factor for AKI. The correct hypothesis of the mechanism between gender and AKI has not been established. However, the renal ischemia-reperfusion injury may be essential in sexual dimorphism.[34] One study suggested that elevation in the BUN-to-SCr ratio could be related to impaired kidney perfusion (prerenal) as the cause of kidney failure in the hospitalized patient.[35] In the ICU setting, septic shock was found to be associated with AKI after colistin treatment.[19] A similar trend of hemodynamic parameters, including SBP and DBP, was observed in the univariable analysis in our study. However, we observed that SBP and DBP showed a U-shaped relationship rather than a linear relationship with the outcome of kidney injury. In addition, the graph exhibited the lowest incidence of AKI with SBP and DBP ranging from 90 to 110 mmHg and 55 to 65 mmHg, respectively (Supplementary Data Figure 1); thus, either too low or too high blood pressure might lead to a worse effect on kidney outcomes. This finding of optimum SBP was consistent with the previous reports[31] and supported by one study that reported that DBP was considered a potential important hemodynamic target for kidney outcomes of sepsis patients.[31] Another study suggested that colistin pharmacokinetics could induce AKI if the hemodynamics were compromised.[36] Although a previous study in critically ill patients found that a loading dose of colistin was associated with an increase in survival at 30 days but also increased the risk of nephrotoxicity[18], we did not find a similar renal outcome in our study that had a lower baseline SCr and lower proportion of patients with shock.

In the univariable analysis of our study, two parameters were found to be associated with AKI, similar to a previous study including diabetes mellitus[9,10,12,14,15] and initial serum creatinine[16], but were eventually excluded from the final model. In contrast to earlier studies, we did not find a significant association between AKI and age[8,12-15], preexisting organ dysfunctions (renal disease[16,22], liver disease[12,13]), colistin dosage[10,12], concomitant nephrotoxic agents[10], scoring system (Charlson's comorbidity index[12,16], APACHE II[17,18], SAPS II[19,20,22]). The explanation of these different findings might be due to the sample size of this study being too small to detect those parameters, especially universal predictors like age, or the small proportions of preexisting

renal and liver disease and concomitant nephrotoxic drugs in our study. The higher SAPS II[19,20,22] and APACHE II scores[18] were reported to be associated with AKI in the studies of critically ill patients in an ICU; thus, this finding possibly supports the 75% of patients in this study that stayed in the ICU. A recent study in a university hospital in Thailand showed a good overall performance of a scoring system (based on age >60 years, comorbidities, serum albumin less than 3.5 g/dL, and concomitant nephrotoxic agent) for predicting patients at high risk of colistin-associated nephrotoxicity.[37] The different predicting variables between this study and our study might be due to our study limiting the patients to only those with AB-VAP, as we had higher in-hospital mortality but fewer patient with comorbidities or concomitant nephrotoxic agents.

Colistin-induced nephrotoxicity mechanisms are related to an increase in tubular epithelial cell membrane permeability, leading to cell swelling and lysis and dilatation of renal tubules, cast formation, and tubular necrosis.[38] Another study suggested that these effects could be associated with the concentration and length of exposure to colistin.[39] Other studies reported that lower daily doses per IBW were associated with increased mortality.[12] However, in our study, there was no significant difference in the mean daily dosages between AKI and non-AKI patients. Nevertheless, we noticed that the AKI group tended to have higher proportions of over-and underdosing of colistin administration.

This study had several limitations. First, as a pilot study, the sample size was too small to detect many important potential predictors, but the performance was still fair. Second, our study was a retrospective observational study; thus, the regimens of colistin were varied, and there was no colistin plasma level monitoring. A previous study reported that the trough level of plasma colistin might be related to nephrotoxicity.[40] Finally, as a single centre study, the generalizability is limited and an external model validation study is required in the future. Thus, we are planning for a following larger-scale study to validate this prediction model or scoring system.

Conclusion

We propose a prediction model for acute kidney injury after colistin treatment for multidrug-resistant AB-VAP pneumonia which had fair to good performance. Renal function should be closely monitored during administration of colistin with special attention to certain predictors, notably female gender, ICU admission, high BUN level, and diastolic blood pressure.

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Conflict of interest

None declared.

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Supplementary Data Table 1 Characteristics of 51 study patients with AKI

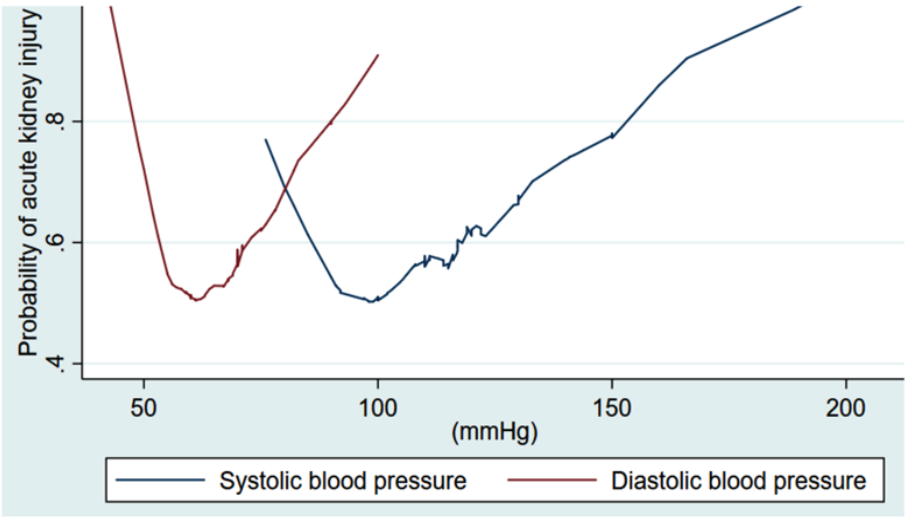
Characteristic	n (%)
KDIGO classification	
Stage 1	3 (6)
Stage 2	2 (4)
Stage 3	46 (90)
RIFLE classification (only AKI <4 weeks)	
Risk	0 (0)
Injury	1 (2)
Failure	50 (98)
Hyperkalaemia	11 (22)
Volume overload	14 (27)
Haemodialysis	6 (12)

AKI=acute kidney injury, KDIGO=Kidney Disease: Improving Global Outcomes, RIFLE=Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

Supplementary Data Table 2 Distribution of AKI vs non-AKI into low, moderate, and high probability categories, the likelihood ratio of positive and 95% confidence intervals

Probability category	Score	AKI (n=51)	Non-AKI (n=34)	LHR+	95% CI	p-value
		n (%)	n (%)			
Low	<120	2 (4)	15 (44)	0.09	0.02, 0.36	<0.001
Moderate	120-180	34 (67)	16 (47)	1.42	0.94, 2.13	0.115
High	>180	15 (29)	3 (9)	3.33	1.04, 10.65	0.030
Mean±S.D.		167±4	129±6			<0.001

AKI=acute kidney injury, LHR=likelihood ratio, CI=confidence interval, S.D.=standard deviatio



Supplementary Data Figure 1